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Title: Exercise dose-response relationship with heart rate variability in individuals with overweight and obesity: Protocol for a systematic review and meta-analysis of randomized controlled trials

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Title: Exercise dose-response relationship with heart rate variability in individuals with overweight and obesity: Protocol for a systematic review and meta-analysis of randomized controlled trials

Abstract:

Objective: To estimate the extent to which exercise doses impacts on heart rate variability (HRV) among individuals living with overweight and obesity class I and II.

Methods: A systematic literature search will be performed using PubMed/Medline, Scopus, EMBASE, ProQuest, CINAHL, Web of Science, and the Cochrane Library for articles dating from 1965 to December 2020. Studies with parallel randomized control trials (RCTs), enrolled adolescent and adult individuals with overweight [BMI ≥ 25 – ≤29.9] and obesity [class I BMI: 30 - 34.9 and class II BMI: 35 - 39.9] undergoing aerobic or resistance training or concurrent exercise training are inclusion requirements. For data synthesis, sensitivity analysis, subgroup analysis, and risk of bias assessment, Stata V.13.0 software will be used.

Key words: cardiac autonomic function, heart rate variability, exercise training, aerobic exercise, resistance exercise, concurrent exercise, physical activity

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Strength and limitation:

- This research will evaluate the impact of exercise (aerobic, resistance, and concurrent training) on HRV in overweight [BMI ≥ 25 to ≤29.9] and obesity [class I BMI: 30 - 34.9 and class II BMI: 35 - 39.9] Uniqueness of this study is focusing on the dose-response analysis of intervention
- Two reviewers will perform data extraction and risk of bias evaluation separately
- There may be a language bias, as only English language article will be included

Introduction:

Over the past 35 years, the global prevalence of obesity has tripled and is expected to rise by over one billion people by 2030 as per the current trend.[1-2] Individuals living with obesity have a significantly high risk of developing cardiovascular disease, diabetes, hypertension, cancer, stroke, and chronic disease, including osteoarthritis.[1] Obesity has also been linked to alteration in cardiac autonomic activity as seen when measuring heart rate variability (HRV).[3-4] Heart rate variability is a non-invasive technique for analyzing autonomic function by measuring beat-to-beat changes in R-R intervals.[5] Low HRV is associated with higher skinfold thickness, higher body mass index (BMI), higher body fat percentages and is an autonomous predictor of cardiovascular mortality and sudden cardiac death.[6-8] In contrast, higher HRV is found to be associated with reduced morbidity, mortality, improved quality of life, and psychological well-being.[9-11]

Earlier studies have reported that obese individuals are relatively more susceptible to ventricular arrhythmias, which in turn was found to be a powerful indicator of sudden death. [12-15] Several researchers have shown decreased HRV in obese people (BMI ≥30) and this suggests that autonomic disturbances could be involved in the processes stimulating

arrhythmia in such people.[16-18] Weight loss by exercise training and dietary intervention, on the other hand, has been shown to reverse the detrimental impact of weight gain on autonomic function.[6-7,18-19]

Benefits of exercise training are documented as a possible non-pharmacological weight-loss approach.[20,21] Exercise in terms of aerobic, resistance, or concurrent are the efficacious means to improve anthropometric indicators of adiposity.[22-24] These exercise types are characterized by multiple sub-divisions such as frequency, intensity, and volume of exercise that may be considered to constitute the exercise "dosage." The effectiveness of the exercise intervention in reducing body weight is documented as dose-dependent and it is mediated by autonomic control.[25-29]

Current evidence on the influence of long-term exercise training on HRV in healthy or obese individuals is inconsistent, with several studies showing significant increase in the HRV following an exercise training with varying dose ranging from 3 weeks to 12 months of exercise training in healthy and obese individuals[7,19,30-33] while other studies did not show such an effect.[34-36] Such differences in effect may be due to either participant attributes, a technique of measurement to estimate HRV, study design, exercise types, and/or exercise dose parameter.[36]

A meta-analysis study[29] in a healthy person over 18 years of age suggested that aerobic exercise training can make substantial improvements in the RR interval, and the effect size for changes in the RR interval recorded in this study was significantly higher in long exercise interventions (>12 weeks) than in shorter treatments (<12 weeks). Also, a meta-analysis in elderly[37] suggested endurance-type exercise is effective for increasing HRV, and exercise frequency appears to be a powerful component of training that decides HRV improvement.

A recent meta-analysis[19] reported improvement in HRV following weight-loss strategies such as dietary approaches, aerobic training, strength training, and exercise programs coupled with dietary approaches. Also, they suggested that the impact of weight loss on the ANS might depend primarily on the amount of weight loss. Differences in the dosage of exercise, such as the duration, frequency, and strength of exercise training, are considered to be responsible for the degree of improvement in autonomic cardiac function and the change in body weight.[19]

The exercise-based weight loss program is known to be part of the key therapy for obesity and recognizing its impact on the HRV will be value-added to the current evidence. In addition, no studies to date have comprehensively analyzed and examined the evidence of exercise dose-response on HRV in people with overweight or obesity. Therefore, the objective of this review is to estimate the extent to which exercise-dose increases heart rate variability in individuals living with overweight and obesity class I and II.

METHODS:

The Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) guidelines are used for the current study.[38] This systematic review will consider only randomized controlled trials (RCTs). This systematic review is registered with PROSPERO (CRD42019104154). Any amendments to this study protocol will be reported.

Electronic Search:

Seven databases will be searched PubMed/Medline, Scopus, EMBASE, ProQuest, CINAHL, Web of Science, and the Cochrane Library, for articles dating from 1965 to December 2020, since Hon and lee[5] published their understanding of the clinical importance of heart rate

variability in 1965. We will also refer to The ClinicalTrials.gov, the International Clinical Trial Registry Platform of the WHO's, the reference list of key articles identified via Scopus, and articles that cited the included articles. Also, authors will be contacted to get aggregate study data that has been completed but not published. If more than one publication describes the same study, the one that provides the most data will be included in the meta-analysis. Studies will be limited to publications in the English language. The search will be carried out by the first author and a medical librarian. Table 1 Shows the search strategy for PubMed.

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((((((((((((((((("exercise"[MeSH Terms]) OR exercise) OR exercise[Text Word]) OR exercise[Title]) OR exercise[Title/Abstract])) OR ((((aerobic exercise) OR aerobic exercise[Text Word]) OR aerobic exercise[Title]) OR aerobic exercise[Title/Abstract])) OR ((((resistance exercise) OR resistance exercise[Text Word]) OR resistance exercise[Title]) OR resistance exercise[Title/Abstract])) OR ((((concurrent exercise) OR concurrent exercise[Text Word]) OR concurrent exercise[Title]) OR concurrent exercise[Title/Abstract])) OR ((((combination exercise) OR combination exercise[Text Word]) OR combination exercise[Title]) OR combination exercise[Title/Abstract])) OR (((((("resistance training"[MeSH Terms]) OR resistance training) OR resistance training[Text Word]) OR resistance training[Title]) OR resistance training[Title/Abstract])) OR ((((aerobic training) OR aerobic training[Text Word]) OR aerobic training[Title]) OR aerobic training[Title/Abstract])) exercise dose OR dose response OR aerobic dose OR resistance dose OR concurrent dose OR combination dose OR (((((("cardiorespiratory fitness"[MeSH Terms]) OR cardiorespiratory fitness[Text Word]) OR cardiorespiratory fitness[Title]) OR

cardiorespiratory fitness[Title/Abstract]) OR cardiorespiratory fitness)) OR ((((physical activity) OR physical activity[Text Word]) OR physical activity[Title]) OR physical activity[Title/Abstract])) OR ((((cardiorespiratory endurence) OR cardiorespiratory endurence[Text Word]) OR cardiorespiratory endurence[Title]) OR cardiorespiratory endurence[Title/Abstract])) OR ((((strength training) OR strength training[Text Word]) OR strength training[Title]) OR strength training[Title/Abstract])) OR ((((strengthening) OR strengthening[Text Word]) OR strengthening[Title]) OR strengthening[Title/Abstract])))

AND

(((((((("overweight"[MeSH Terms]) OR overweight) OR overweight[Text Word]) OR overweight[Title]) OR overweight[Title/Abstract])) OR (((((("obesity"[MeSH Terms]) OR obesity) OR obesity[Text Word]) OR obesity[Title]) OR obesity[Title/Abstract])) OR ((((healthy individuals[Text Word]) OR healthy individuals[Title]) OR healthy individuals[Title/Abstract]) OR healthy individuals)))

AND

(((((((((heart rate variability) OR heart rate variability[Text Word]) OR heart rate variability[Title]) OR heart rate variability[Title/Abstract])) OR ((((autonomic function) OR autonomic function[Text Word]) OR autonomic function[Title]) OR autonomic function[Title/Abstract])) OR ((((sympathetic function) OR sympathetic function[Text Word]) OR sympathetic function[Title]) OR sympathetic function[Title/Abstract])) OR ((((parasympathetic function) OR parasympathetic function[Text Word]) OR parasympathetic function[Title]) OR parasympathetic function[Title/Abstract])) OR ((((vagal function) OR vagal function[Text Word]) OR vagal function[Title]) OR vagal function[Title/Abstract]))

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Eligibility Criteria and Study selection:

The titles and abstracts screening will be done for eligibility and the article considered appropriate will be reviewed in full-text papers. This process will be conducted using Covidence (www.covidence.org). [39]

Inclusion Criteria:

Studies will be included if a) Parallel randomized control trials (RCTs), b) enrolled adolescent (Age≥10 years) and adult individuals with overweight [BMI ≥ 25 – ≤29.9] and obesity [class I BMI: 30 - 34.9 and class II BMI: 35 - 39.9] undergoing aerobic or resistance exercise training or concurrent exercise training (Table 2)[40]

Table 2: Operational definitions of exercises type used for the current systematic review according to The American College of Sports Medicine. [40]

Exercise Type	Operational definition
Aerobic/endurance exercise training-	Aerobic exercise as any activity that uses large muscle groups, can be maintained continuously and is rhythmic in nature
Resistance/strength exercise training	Strength training that involves the performance of physical exercises which are designed to improve muscle strength and endurance
Concurrent exercise training	The combination of muscle strength and aerobic exercise during the same session or training program

and had an outcome of interest as HRV c) exercise intervention is reported in terms of frequency, intensity, time, and type, and d) measurement of at least one variable of HRV before and after the training intervention is reported.

Exclusion Criteria:

Exclusion criteria will be a) observational studies, b) studies measuring acute exercise effects, c) obesity class III (BMI ≥40) as it has been found that individuals living with severe obesity may have impaired autonomic function and this would confound the outcome of interest, and d) studies including individuals with cardiac, neurodegenerative, kidney or metabolic disease as they have an impact on autonomic function.[37,41-42]

Study Selection:

Following different database searches, retrieved articles will be imported to Covidence platform[39] where the results will be combined and duplicates will be removed. As a large number of papers are expected to do the screening, four authors will be involved in the screening and pilot-tested on the first 10 % of titles and abstracts for the eligibility criteria. To harmonize the screening process, a training session will be provided to all reviewers. During this session reviewer will be asked to pilot-screen 15 titles/abstracts to prompt clarifications and screening decisions will be taken in compliance with inclusion/exclusion criteria. After scanning for titles and abstracts, articles that do not meet the inclusion requirements will be excluded and the remaining articles will have their full-text versions retrieved. The full-text screening will be done by two lead members of the synthesis team using the level of agreement between reviewers. Kappa statistics will be used to test the agreement [i.e. thresholds: <0.20 slight agreement, 0.21 - 0.40 fair agreement, 0.41 - 0.60 moderate agreement, 0.61 - 0.80 substantial agreement and >0.80 almost perfect agreement].[43] Disputes will be settled by agreement with the reviewers or by contacting an adjudicator. In a PRISMA flow chart, the study selection process is displayed.[44](Figure I)

Data extraction and analysis:

Outcomes:

In this study, the primary outcome of interest is the time domain (SDNN, SDANN, RMSSD, pNN50) and frequency domain variables of HRV (Total power, VLF, LF, HF, LF/HF ratio). (Table 3)

Table 3: Heart rate variability Domains.[5]

Time domain measures of HRV: Variable(units) and description	
SDNN (ms)	Standard deviation of all NN intervals
SDANN (ms)	Standard deviation of the averages of NN intervals
RMSSD (ms)	The square root of the mean of the sum of the squares of differences between adjacent NN intervals
pNN50 %	NN50 count divided by the total number of all NN intervals
Frequency domain measures of HRV: Variable(units) and description	
Total power ms^2	The variation of NN intervals over the temporal segment
VLF (ms^2)	Power in very low frequency range
LF (ms^2)	Power in low frequency range
HF (ms^2)	Power in high frequency range
LF/HF ratio	Ratio of LF and HF

Cardiorespiratory endurance, muscular strength, adiposity/anthropometric measures are the secondary outcome of interest. These outcomes are chosen based on the previous research.[7,19,30-33] If data are available in qualifying studies, the relationship of exercise training with other endpoints, such as time effect and interaction effect with

sociodemographic variables, anthropometric measures, presence of cardiovascular risk factors, diet, exercise adherence, and life stress, will also be analyzed.

Data extraction:

A data extraction form will be adopted from published literature.[45-47] Data extraction process consists of manuscript title, author, time of publication, source of literature, characteristics of the trial (author, conducted/ publication year, duration, place of the trial conducted, number of participating centers, study design), the participants (sample size, participants randomized and patients analyzed in each group, age, sex, socioeconomic status, height, weight, body mass index, waist circumference, waist-hip ratio, waist-height ratio, and body fat percent), intervention (aerobic, resistance, and concurrent exercise dose in terms of frequency, intensity, number of sessions, duration, and progression), control group treatment, method of randomization, method of allocation, blinding process, outcome time point and follow- up period, lack of follow-up or withdrawal, any incidental findings reported and the main outcome measurement heart rate variability reported either in absolute or log transformed or both. Two independent reviewers will be pilot-testing the data extraction form and to resolve any disagreements team meetings will be conducted to refine the form. The two reviewers will perform data extraction separately. A training session will be held to harmonize the extraction of data, and at least two pilot extractions will be carried out to ensure accuracy. A written 'Data Extraction Guide' with detailed instructions will also be provided to reviewers. To assure accuracy, one lead member of the systematic review team will extract data from each article. An impartial third reviewer will cross-check the data extracted in duplicate. Inconsistencies in the data obtained will be resolved by agreement between the reviewers after reviewing the full-text article. When

discrepancies occur, an adjudicator will be contacted. If the data published is incomplete or vague, the authors of the research will be contacted. Data extraction will be independently cross-checked.

Quality and Risk of bias assessment:

Two reviewers will independently review each selected article to eliminate bias. All selected articles will be evaluated for their quality based on the Cochrane Collaboration's Risk of Bias Tool 2.0 (RoB 2.0)[48] for risk of bias assessment across five domains. Assessments will be carried out using an iterative online form available.[49] The domain of missing outcome data will be evaluated, as per Akobeng and Ebrahim.[50-51] For each domain, the probability of bias will be evaluated as 'low risk',' some concerns', or 'high risk'. If at least one area is listed as 'high risk,' studies will be deemed to have an overall high risk of bias. Quality of evidence will be measured using the GRADE rating system.[52] Publication bias will be evaluated using visual inspection of funnel plot asymmetry. [53]

Data synthesis Strategy: Meta-analysis:

We will primarily examine the training effect (aerobic, resistance, and concurrent exercise training) on HRV. We will also explore possible sources of heterogeneity among studies by examining aerobic, resistance, and concurrent exercise impact with time point. To attain the standardized mean difference and 95% confidence interval, the data of interest given as continuous will be used for meta-analysis. The Q-statistic and I^2 tests will be used to test for heterogeneity between the included studies. Heterogeneity will be considered low if I^2 is ≤ 40%, and high if I^2 is ≥ 75%. We will use a random-effects model for meta-analysis If

substantial heterogeneity (I^2 >40 %) or fixed effects for homogeneous effects (I^2 <40%).[54] Aggregate data obtained from the included studies will be used for quantitative synthesis. By plotting the data on a forest plot, heterogeneity will be evaluated visually.[55]

Analysis of subgroups or subsets:

The sub-analysis will include baseline participant characteristics and exercise intervention characteristics. Interaction effects between variables will be identified for subgroup analysis.[55]

Significance:

Due to modernization and mechanization of lifestyle, there is an increase in overweight and obesity globally. Exercise is a key element to prevent lifestyle disease, therefore it is important to explore dose-response benefits specifically towards heart rate variability to maximize the physiological benefits. The study would help to understand the autonomic response of the heart (i.e., heart rate variability) at different doses of exercise training. Also can help to recommend the training regimen for overweight and obese people for optimum gain in heart rate variability

Ethics and dissemination:

This review will not require an ethical authorization, since participant privacy issues do not exist. Our results will provide data on the various forms of exercise dose-response on the HRV in overweight and obese people. The results of this study will be published in a peer-reviewed international journal, displayed at relevant conferences, and disseminated to obesity-focused public organizations.

Contributors:

All the authors conceived the idea for this systematic review and developed the protocol, drafted the manuscript, revised the manuscript for important intellectual content, and drafted the final version systematic review protocol manuscript for submission. All the contributors read and approved the final manuscript.

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Competing interests: None

Patient consent for publication: not required

Availability of data and materials: For this study, data sharing is not applicable.

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Figure 1: Flow diagram for study selection based on the PRISMA guidelines: (Moher, Liberati, Tetzlaff, & Altman, 2009)

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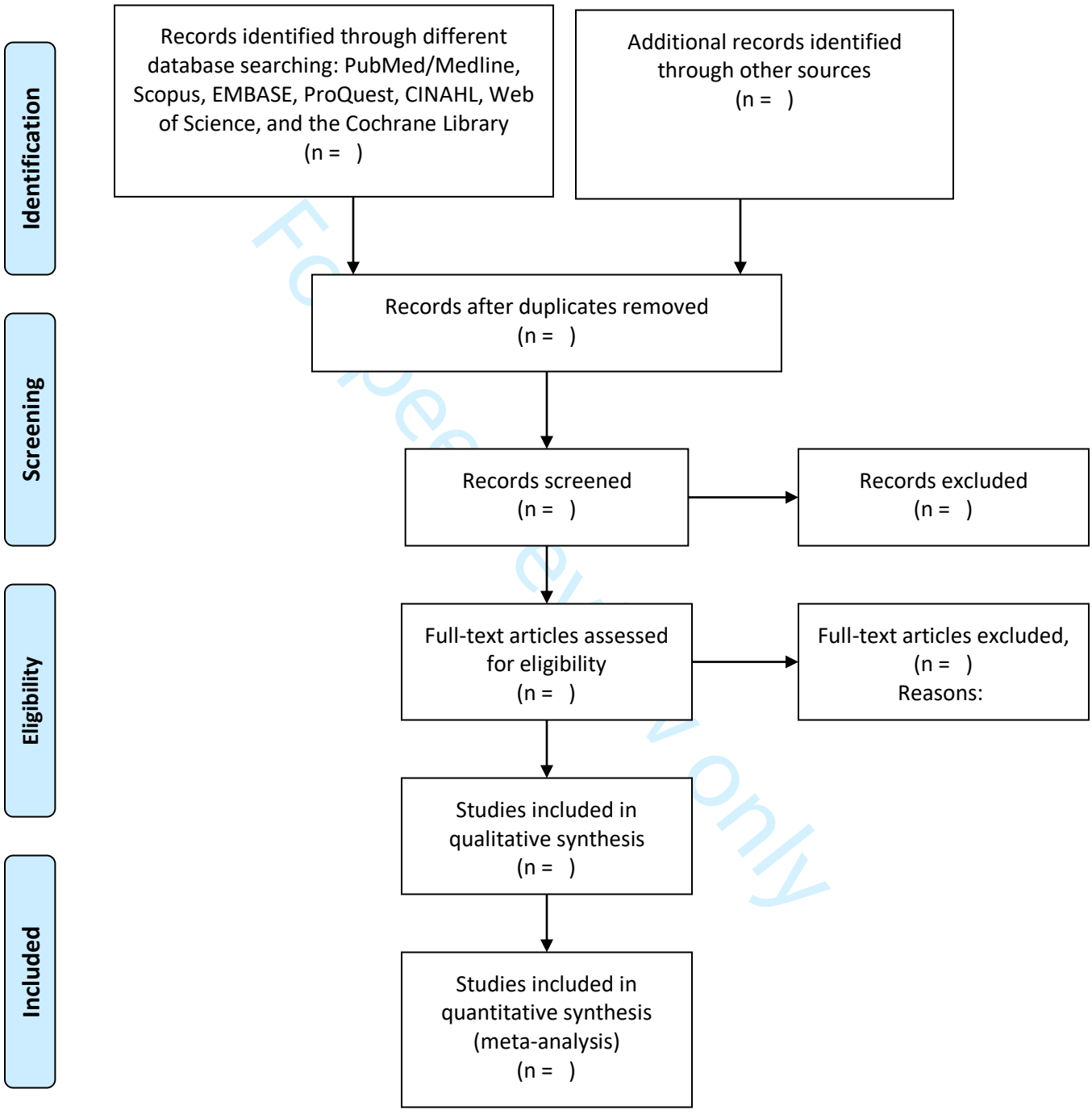

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

Reporting checklist for protocol of a systematic review.

Title: Exercise dose-response relationship with heart rate variability in individuals with overweight and obesity: Protocol for a systematic review and meta-analysis of randomized controlled trials

Based on the PRISMA-P guidelines.

		Reporting Item	Page Number
Identification	#1a	Identify the report as a protocol of a systematic review	1
Update	#1b	If the protocol is for an update of a previous systematic review, identify as such	NA
	#2	If registered, provide the name of the registry (such as PROSPERO) and registration number	2
Contact	#3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1& 2
Contribution	#3b	Describe contributions of protocol authors and identify the guarantor of the review	14
	#4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important	NA

		protocol amendments	
Sources	#5a	Indicate sources of financial or other support for the review	14
Sponsor	#5b	Provide name for the review funder and / or sponsor	NA
Role of sponsor or funder	#5c	Describe roles of funder(s), sponsor(s), and / or institution(s), if any, in developing the protocol	NA
Rationale	#6	Describe the rationale for the review in the context of what is already known	3-5
Objectives	#7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	5
Eligibility criteria	#8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	5-9
Information sources	#9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	5-9
Search strategy	#10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	5-7
Study records - data management	#11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	9-10
Study records - selection process	#11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	9
Study records - data collection process	#11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	10-12
Data items	#12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	10-11

Outcomes and prioritization	#13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	10-11
Risk of bias in individual studies	#14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	12
Data synthesis	#15a	Describe criteria under which study data will be quantitatively synthesized	12-13
	#15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I2, Kendall's τ)	12-13
	#15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	13
	#15d	If quantitative synthesis is not appropriate, describe the type of summary planned	12-13
Meta-bias(es)	#16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	12
Confidence in cumulative evidence	#17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	12

BMJ Open

Exercise dose-response relationship with heart rate variability in individuals with overweight and obesity: Protocol for a systematic review and meta-analysis of randomized controlled trials

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Title: Exercise dose-response relationship with heart rate variability in individuals with overweight and obesity: Protocol for a systematic review and meta-analysis of randomized controlled trials

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Title: Exercise dose-response relationship with heart rate variability in individuals with overweight and obesity: Protocol for a systematic review and meta-analysis of randomized controlled trials

Abstract:

Objective: To estimate the extent to which exercise doses impacts on heart rate variability (HRV) among individuals living with overweight and obesity class I and II.

Methods: A systematic literature search will be performed using PubMed/Medline, Scopus, EMBASE, ProQuest, CINAHL, Web of Science, and the Cochrane Library for articles dating from 1965 to December 2020. Inclusion criteria include studies designed as parallel-arm randomized trials, enrolling adolescent and adult individuals with overweight [BMI ≥ 25 – ≤29.9] and obesity [class I BMI: 30 - 34.9 and class II BMI: 35 - 39.9] undergoing aerobic or resistance training or concurrent exercise training. For data synthesis, sensitivity analysis, subgroup analysis, and risk of bias assessment, Stata V.13.0 software will be used.

Key words: cardiac autonomic function, heart rate variability, exercise training, aerobic exercise, resistance exercise, concurrent exercise, physical activity

PROSPERO Registry no: CRD42019104154

Strength and limitation:

- Strength of the design is the focus on dose-response analysis of intervention
- Two reviewers will perform data extraction and risk of bias evaluation separately
- Only English language article will be included

Introduction:

Over the past 35 years, the global prevalence of obesity has tripled and current trends, if extrapolated would lead to approximately over one billion people by 2030.[1-2] Individuals living with obesity have a significantly higher risk of developing cardiovascular disease, diabetes, hypertension, cancer, stroke, and chronic disease, including osteoarthritis.[1] Obesity has also been linked to alteration in cardiac autonomic activity as seen when measuring heart rate variability (HRV).[3-4] Heart rate variability is a non-invasive technique for analyzing autonomic function by measuring beat-to-beat changes in R-R intervals of electrocardiogram (ECG) signals.[5] Low HRV is associated with higher skinfold thickness, higher body mass index (BMI), higher body fat percentages and is an autonomous predictor of cardiovascular mortality and sudden cardiac death.[6-8] In contrast, higher HRV is found to be associated with reduced morbidity, mortality, improved quality of life, and psychological well-being.[9-11]

Earlier studies have reported that obese individuals are relatively more susceptible to ventricular arrhythmias, which has been found to be a powerful indicator of sudden death. [12-15] Several researchers have shown decreased HRV in obese people (BMI ≥30) and this suggests that autonomic disturbances could be involved in the processes stimulating arrhythmia in such people.[16-18] Weight loss by exercise training and dietary intervention, on

the other hand, has been shown to reverse the detrimental impact of weight gain on autonomic function.[6-7,18-19]

Benefits of exercise training are documented as a possible non-pharmacological weight-loss approach.[20,21] All forms of exercise, whether aerobic, resistance, or combination of aerobic and resistance (concurrent), are effective methods of improving anthropometric indicators of adiposity.[22-24] These exercise types are characterized by multiple sub-divisions such as frequency, intensity, and volume of exercise that may be considered to constitute the exercise "dosage." The effectiveness of the exercise intervention in reducing body weight is documented as dose-dependent and it is mediated by autonomic control.[25-29]

Current evidence on the influence of long-term exercise training on HRV in healthy or obese individuals is inconsistent, with several studies showing significant increase in the HRV following an exercise training with varying dose ranging from 3 weeks to 12 months of exercise training in healthy and obese individuals[7,19,30-33] while other studies did not show such an effect.[34-36] Such differences in effect may be due to either participant attributes, a technique of measurement to estimate HRV, study design, exercise types, and/or exercise dose parameter.[36]

A meta-analysis done using data from studies carried out in healthy people suggested that aerobic exercise training can make substantial improvements in the RR interval, and the effect size for changes in the RR interval recorded in this study was significantly higher in long exercise interventions (>12 weeks) than in shorter treatments (<12 weeks).[29] Meta-analysis including studies done in the elderly [37] suggested endurance-type exercise is effective for increasing HRV, and exercise frequency appears to be a powerful component of training that leads to HRV improvement.

A recent meta-analysis[19] reported improvement in HRV following weight-loss strategies such as dietary approaches, aerobic training, strength training, and exercise programs coupled with dietary approaches. Also, this study suggested that the impact of weight loss on the ANS might depend primarily on the amount of weight loss. Differences in the dosage of exercise, such as the duration, frequency, and strength of exercise training, are considered to be responsible for the degree of improvement in autonomic cardiac function and the change in body weight.[19]

The Exercise-based weight loss programs are known to be a key part of therapy for obesity and evaluating its impact on HRV would add value to current assessments of the evidence base. In addition, no studies to date have comprehensively analyzed and examined the evidence of exercise dose-response on HRV in people with overweight or obesity. Therefore, the objective of this review is to estimate the extent to which exercise-dose increases heart rate variability in individuals living with overweight and obesity class I and II.

METHODS:

The Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) guidelines are used for the current study. PRISMA will be used to assist reporting of the SR, once completed.[38] This systematic review will consider only randomized controlled trials (RCTs). This systematic review is registered with PROSPERO (CRD42019104154). Any amendments to this study protocol will be reported.

Electronic Search:

Seven databases will be searched; PubMed/Medline, Scopus, EMBASE, ProQuest, CINAHL, Web of Science, and the Cochrane Library, for articles dating from 1965 to December 2020,

since Hon and Lee[5] published their understanding of the clinical importance of heart rate variability in 1965. We will also refer to clinicaltrials.gov, the World Health Organization's registry platform ICTRP, the reference lists of key articles identified via Scopus, and articles that cited the included articles. Also, authors will be contacted to obtain for studies that have been completed but not published. If more than one publication describes the same study, the one that provides the most data will be included in the meta-analysis. Studies will be limited to publications in the English language. The search will be carried out by the first author and a medical librarian. Table 1 Shows the search strategy for PubMed.

Table 1 Shows the search strategy for PubMed

((((((((((((((((("exercise"[MeSH Terms]) OR exercise) OR exercise[Text Word]) OR exercise[Title]) OR exercise[Title/Abstract])) OR ((((aerobic exercise) OR aerobic exercise[Text Word]) OR aerobic exercise[Title]) OR aerobic exercise[Title/Abstract])) OR ((((resistance exercise) OR resistance exercise[Text Word]) OR resistance exercise[Title]) OR resistance exercise[Title/Abstract])) OR ((((concurrent exercise) OR concurrent exercise[Text Word]) OR concurrent exercise[Title]) OR concurrent exercise[Title/Abstract])) OR ((((combination exercise) OR combination exercise[Text Word]) OR combination exercise[Title]) OR combination exercise[Title/Abstract])) OR (((((("resistance training"[MeSH Terms]) OR resistance training) OR resistance training[Text Word]) OR resistance training[Title]) OR resistance training[Title/Abstract])) OR ((((aerobic training) OR aerobic training[Text Word]) OR aerobic training[Title]) OR aerobic training[Title/Abstract])) exercise dose OR dose response OR aerobic dose OR resistance dose OR concurrent dose OR combination dose OR (((((("cardiorespiratory fitness"[MeSH Terms]) OR cardiorespiratory fitness[Text Word]) OR cardiorespiratory fitness[Title]) OR

cardiorespiratory fitness[Title/Abstract]) OR cardiorespiratory fitness)) OR ((((physical activity) OR physical activity[Text Word]) OR physical activity[Title]) OR physical activity[Title/Abstract])) OR ((((cardiorespiratory endurence) OR cardiorespiratory endurence[Text Word]) OR cardiorespiratory endurence[Title]) OR cardiorespiratory endurence[Title/Abstract])) OR ((((strength training) OR strength training[Text Word]) OR strength training[Title]) OR strength training[Title/Abstract])) OR ((((strengthening) OR strengthening[Text Word]) OR strengthening[Title]) OR strengthening[Title/Abstract])))

AND

(((((((("overweight"[MeSH Terms]) OR overweight) OR overweight[Text Word]) OR overweight[Title]) OR overweight[Title/Abstract])) OR (((((("obesity"[MeSH Terms]) OR obesity) OR obesity[Text Word]) OR obesity[Title]) OR obesity[Title/Abstract])) OR ((((healthy individuals[Text Word]) OR healthy individuals[Title]) OR healthy individuals[Title/Abstract]) OR healthy individuals)))

AND

(((((((((heart rate variability) OR heart rate variability[Text Word]) OR heart rate variability[Title]) OR heart rate variability[Title/Abstract])) OR ((((autonomic function) OR autonomic function[Text Word]) OR autonomic function[Title]) OR autonomic function[Title/Abstract])) OR ((((sympathetic function) OR sympathetic function[Text Word]) OR sympathetic function[Title]) OR sympathetic function[Title/Abstract])) OR ((((parasympathetic function) OR parasympathetic function[Text Word]) OR parasympathetic function[Title]) OR parasympathetic function[Title/Abstract])) OR ((((vagal function) OR vagal function[Text Word]) OR vagal function[Title]) OR vagal function[Title/Abstract]))

130

Eligibility Criteria and Study selection:

The titles and abstracts screening will be done for eligibility and the article considered appropriate will be reviewed in full-text papers. This process will be conducted using Covidence (www.covidence.org)[39] and it is expected to be completed by December 2021.

Inclusion Criteria:

Studies will be included if they report data from a) parallel-arm randomized trials (RCTs), b) enrolled adolescent (Age≥10 years) and adult individuals with overweight [BMI ≥ 25 – ≤29.9] and obesity [class I BMI: 30 - 34.9 and class II BMI: 35 - 39.9] undergoing aerobic or resistance exercise training or concurrent exercise training (Table 2)[40]

Table 2: Operational definitions of exercises type used for the current systematic review according to The American College of Sports Medicine. [40]

Exercise Type	Operational definition
Aerobic/endurance exercise training-	Aerobic exercise as any activity that uses large muscle groups, can be maintained continuously and is rhythmic in nature
Resistance/strength exercise training	Strength training that involves the performance of physical exercises which are designed to improve muscle strength and endurance
Concurrent exercise training	The combination of muscle strength and aerobic exercise during the same session or training program

and had an outcome of interest as HRV c) exercise intervention is reported in terms of frequency, intensity, time, and type, and d) measurement of at least one variable of HRV before and after the training intervention is reported.

Exclusion Criteria:

Exclusion criteria will be a) observational studies, b) studies measuring acute exercise effects, c) obesity class III (BMI ≥40) as it has been found that individuals living with severe obesity may have impaired autonomic function and this would confound the outcome of interest, and d) studies including individuals with cardiac, neurodegenerative, kidney or metabolic disease as they have an impact on autonomic function.[37,41-42]

Study Selection:

Following different database searches, retrieved articles will be imported to the Covidence platform[39] where the results will be combined and duplicates will be removed. As a large number of papers are expected to require screening, four authors will be involved in screening. These authors will also perform pilot-testing of eligibility criteria on the first 10% of titles and abstracts. To harmonize the screening process, a training session will be provided to all reviewers. During this session reviewer will be asked to pilot-screen 15 titles/abstracts to prompt clarifications and screening decisions will be taken in compliance with inclusion/exclusion criteria. After scanning for titles and abstracts, articles that do not meet the inclusion requirements will be excluded and the remaining articles will have their full-text versions retrieved. The full-text screening will be done by two lead members of the synthesis team using the level of agreement between reviewers. Kappa statistics will be used to test the agreement [i.e. thresholds: <0.20 slight agreement, 0.21 - 0.40 fair agreement, 0.41 - 0.60 moderate agreement, 0.61 - 0.80 substantial agreement and >0.80 almost perfect agreement].[43] Disputes will be settled by agreement with the reviewers or by contacting an adjudicator. In a PRISMA flow chart, the study selection process is displayed.[44](Figure I)

Data extraction and analysis:

Outcomes:

In this study, the primary outcome of interest is the time domain (SDNN, SDANN, RMSSD, pNN50) and frequency domain variables of HRV (Total power, VLF, LF, HF, LF/HF ratio). (Table 3)

Table 3: Heart rate variability Domains.[5]

Time domain measures of HRV: Variable(units) and description	
SDNN (ms)	Standard deviation of all NN intervals
SDANN (ms)	Standard deviation of the averages of NN intervals
RMSSD (ms)	The square root of the mean of the sum of the squares of differences between adjacent NN intervals
pNN50 %	NN50 count divided by the total number of all NN intervals
Frequency domain measures of HRV: Variable(units) and description	
Total power ms^2	The variation of NN intervals over the temporal segment
VLF (ms^2)	Power in very low frequency range
LF (ms^2)	Power in low frequency range
HF (ms^2)	Power in high frequency range
LF/HF ratio	Ratio of LF and HF

Secondary outcomes include Cardiorespiratory endurance, muscular strength, adiposity/anthropometric measures. These outcomes are chosen based on the previous research.[7,19,30-33] If data are available in qualifying studies, the relationship of exercise training with other endpoints, such as time effect and interaction effect with

sociodemographic variables, anthropometric measures, presence of cardiovascular risk factors, diet, exercise adherence, and life stress, will also be analyzed.

Data extraction:

A data extraction form will be adopted from published literature.[45-47] Data extraction process consists of manuscript title, author, time of publication, source of literature, characteristics of the trial (author, conducted/ publication year, duration, place of the trial conducted, number of participating centers, study design), the participants (sample size, participants randomized and patients analyzed in each group, age, sex, socioeconomic status, height, weight, body mass index, waist circumference, waist-hip ratio, waist-height ratio, and body fat percent), intervention (aerobic, resistance, and concurrent exercise dose in terms of frequency, intensity, number of sessions, duration, and progression), control group treatment, method of randomization, method of allocation, blinding process, outcome time point and follow- up period, lack of follow-up or withdrawal, any incidental findings reported and the main outcome measurement heart rate variability reported either in absolute or log transformed or both. Two independent reviewers will pilot test the data extraction form and to resolve any disagreements team meetings will be conducted to refine the form. The two reviewers will perform data extraction separately. A training session will be held to harmonize the extraction of data, and at least two pilot extractions will be carried out to ensure accuracy. A written 'Data Extraction Guide' with detailed instructions will also be provided to reviewers. To assure accuracy, one lead member of the systematic review team will extract data from each article. An impartial third reviewer will cross-check the data extracted in duplicate. Inconsistencies in the data obtained will be resolved by agreement between the reviewers after reviewing the full-text article. When

discrepancies occur, an adjudicator will be contacted. If the data published is incomplete or vague, the authors of the research will be contacted. Data extraction will be independently cross-checked.

Quality and Risk of bias assessment:

Two reviewers will independently review each selected article to eliminate bias. All selected articles will be evaluated for their quality based on the Cochrane Collaboration's Risk of Bias Tool 2.0 (RoB 2.0)[48] for risk of bias assessment across five domains. Assessments will be carried out using an iterative online form available.[49] The domain of missing outcome data will be evaluated, as per Akobeng and Ebrahim.[50-51] For each domain, the probability of bias will be evaluated as 'low risk',' some concerns', or 'high risk'. If at least one area is listed as 'high risk,' studies will be deemed to have an overall high risk of bias. Quality of evidence will be measured using the GRADE rating system.[52] Publication bias will be evaluated using visual inspection of funnel plot asymmetry. [53]

Data synthesis Strategy: Meta-analysis:

We will primarily examine the training effect (aerobic, resistance, and concurrent exercise training) on HRV. We will also explore possible sources of heterogeneity among studies by examining aerobic, resistance, and concurrent exercise impact with time point. To attain the standardized mean difference and 95% confidence interval, the data of interest given as continuous will be used for meta-analysis. The Q-statistic and I^2 tests will be used to test for heterogeneity between the included studies. Heterogeneity will be considered low if I^2 is ≤ 40%, and high if I^2 is ≥ 75%. We will use a random-effects model for meta-analysis If

substantial heterogeneity (I^2 >40 %) or fixed effects for homogeneous effects (I^2 <40%).[54] Aggregate data obtained from the included studies will be used for quantitative synthesis. By plotting the data on a forest plot, heterogeneity will be evaluated visually.[55]

Analysis of subgroups or subsets:

The sub-analysis will include baseline participant characteristics and exercise intervention characteristics. Interaction effects between variables will be identified for subgroup analysis.[55]

Significance:

Due to modernization and mechanization of lifestyle, there is an increase in overweight and obesity globally. Exercise is a key element to prevent lifestyle disease, therefore it is important to explore dose-response benefits specifically towards heart rate variability to maximize the physiological benefits. The study would help to understand the autonomic response of the heart (i.e., heart rate variability) at different doses of exercise training. Also can help to recommend the training regimen for overweight and obese people for optimum gain in heart rate variability

Ethics and dissemination:

This review will not require an ethical authorization, since participant privacy issues do not exist. Our results will provide data on the various forms of exercise dose-response on the HRV in overweight and obese people. The results of this study will be published in a peer-reviewed international journal, displayed at relevant conferences, and disseminated to obesity-focused public organizations.

Patient and Public Involvement:

No patient involved

Contributors:

SMK, KV, MA and MGA conceived of the study and provided guidance for drafting the protocol. MA and SMK designed the search strategy. SMK, KV, MA, KNS, SNR and MGA drafted and reviewed the final version systematic review protocol manuscript for submission. All the contributors read and approved the final manuscript.

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Competing interests: None

Patient consent for publication: not required

Availability of data and materials: For this study, data sharing is not applicable.

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Figure 1: Flow diagram for study selection based on the PRISMA guidelines: (Moher, Liberati, Tetzlaff, & Altman, 2009)

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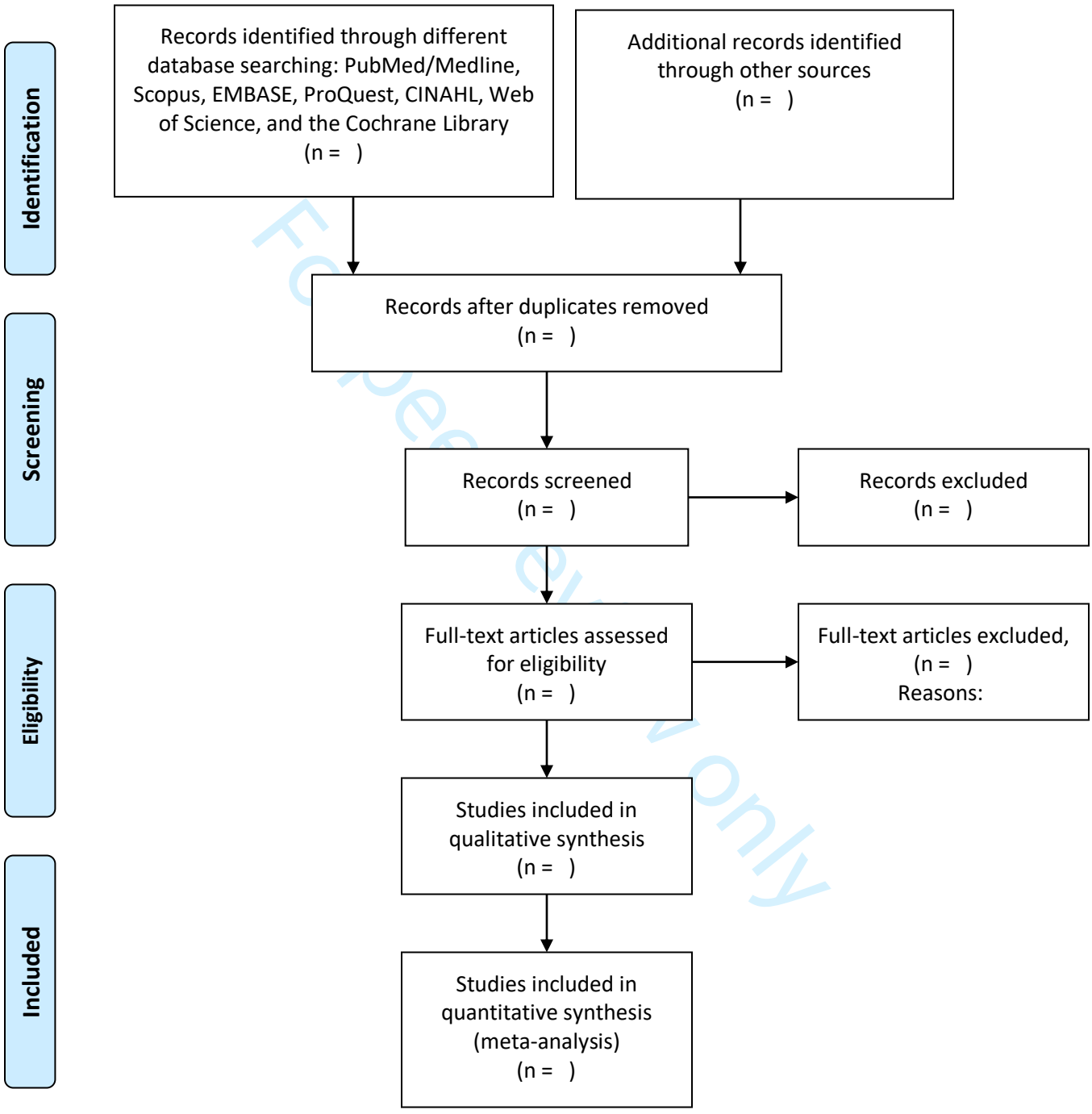

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

Reporting checklist for protocol of a systematic review.

Title: Exercise dose-response relationship with heart rate variability in individuals with overweight and obesity: Protocol for a systematic review and meta-analysis of randomized controlled trials

Based on the PRISMA-P guidelines.

		Reporting Item	Page Number
Identification	#1a	Identify the report as a protocol of a systematic review	1
Update	#1b	If the protocol is for an update of a previous systematic review, identify as such	NA
	#2	If registered, provide the name of the registry (such as PROSPERO) and registration number	2
Contact	#3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1& 2
Contribution	#3b	Describe contributions of protocol authors and identify the guarantor of the review	14
	#4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important	NA

		protocol amendments	
Sources	#5a	Indicate sources of financial or other support for the review	14
Sponsor	#5b	Provide name for the review funder and / or sponsor	NA
Role of sponsor or funder	#5c	Describe roles of funder(s), sponsor(s), and / or institution(s), if any, in developing the protocol	NA
Rationale	#6	Describe the rationale for the review in the context of what is already known	3-5
Objectives	#7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	5
Eligibility criteria	#8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	5-9
Information sources	#9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	5-9
Search strategy	#10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	5-7
Study records - data management	#11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	9-10
Study records - selection process	#11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	9
Study records - data collection process	#11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	10-12
Data items	#12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	10-11

Outcomes and prioritization	#13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	10-11
Risk of bias in individual studies	#14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	12
Data synthesis	#15a	Describe criteria under which study data will be quantitatively synthesized	12-13
	#15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I2, Kendall's τ)	12-13
	#15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	13
	#15d	If quantitative synthesis is not appropriate, describe the type of summary planned	12-13
Meta-bias(es)	#16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	12
Confidence in cumulative evidence	#17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	12

BMJ Open

Exercise dose-response relationship with heart rate variability in individuals with overweight and obesity: Protocol for a systematic review and meta-analysis of randomized controlled trials

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Title: Exercise dose-response relationship with heart rate variability in individuals with overweight and obesity: Protocol for a systematic review and meta-analysis of randomized controlled trials

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Title: Exercise dose-response relationship with heart rate variability in individuals with overweight and obesity: Protocol for a systematic review and meta-analysis of randomized controlled trials

Abstract:

Introduction: Obesity is a chronic relapsing disease process and serious public health concern that can lead to chronic diseases, medical complications, and a higher risk of disability. Another significant feature of obesity is dysfunction in cardiac autonomic function, which leads to changes in parasympathetic and sympathetic regulation, which can be measured using heart rate variability. The objective of this review is to estimate the extent to which exercise doses impacts on heart rate variability (HRV) among individuals living with overweight and obesity class I and II.

Methods and analysis: A systematic literature search will be performed using PubMed/Medline, Scopus, EMBASE, ProQuest, CINAHL, Web of Science, and the Cochrane Library for articles dating from 1965 to December 2021. Inclusion criteria include studies designed as parallel-arm randomized trials, enrolling adolescent and adult individuals with overweight [BMI ≥ 25 – ≤29.9] and obesity [class I BMI: 30 - 34.9 and class II BMI: 35 - 39.9] undergoing aerobic or resistance training or concurrent exercise training. For data synthesis,

sensitivity analysis, subgroup analysis, and risk of bias assessment, Stata V.13.0 software will be used.

Ethics and dissemination: Formal ethical approval is not required. This systematic review will be submitted to a peer-reviewed journal.

Key words: cardiac autonomic function, heart rate variability, exercise training, aerobic exercise, resistance exercise, concurrent exercise, physical activity

PROSPERO Registry no: CRD42019104154

Strength and limitation:

- Strength of the design is the focus on dose-response analysis of intervention
- Two reviewers will perform data extraction and risk of bias evaluation separately
- Only English language article will be included

Introduction:

Over the past 35 years, the global prevalence of obesity has tripled and current trends, if extrapolated would lead to approximately over one billion people by 2030.[1-2] Individuals living with obesity have a significantly higher risk of developing cardiovascular disease, diabetes, hypertension, cancer, stroke, and chronic disease, including osteoarthritis.[1] Obesity has also been linked to alteration in cardiac autonomic activity as seen when measuring heart rate variability (HRV).[3-4] Heart rate variability is a non-invasive technique for analyzing autonomic function by measuring beat-to-beat changes in R-R intervals of electrocardiogram (ECG) signals.[5] Low HRV is associated with higher skinfold thickness, higher body mass index (BMI), higher body fat percentages and is an autonomous predictor of cardiovascular mortality and sudden cardiac death.[6-8] In contrast, higher HRV is found to

be associated with reduced morbidity, mortality, improved quality of life, and psychological well-being.[9-11]

Earlier studies have reported that obese individuals are relatively more susceptible to ventricular arrhythmias, which has been found to be a powerful indicator of sudden death. [12-15] Several researchers have shown decreased HRV in obese people (BMI ≥30) and this suggests that autonomic disturbances could be involved in the processes stimulating arrhythmia in such people.[16-18] Weight loss by exercise training and dietary intervention, on the other hand, has been shown to reverse the detrimental impact of weight gain on autonomic function.[6-7,18-19]

Benefits of exercise training are documented as a possible non-pharmacological weight-loss approach.[20,21] All forms of exercise, whether aerobic, resistance, or combination of aerobic and resistance (concurrent), are effective methods of improving anthropometric indicators of adiposity.[22-24] These exercise types are characterized by multiple sub-divisions such as frequency, intensity, and volume of exercise that may be considered to constitute the exercise "dosage." The effectiveness of the exercise intervention in reducing body weight is documented as dose-dependent and it is mediated by autonomic control.[25-29]

Current evidence on the influence of long-term exercise training on HRV in healthy or obese individuals is inconsistent, with several studies showing significant increase in the HRV following an exercise training with varying dose ranging from 3 weeks to 12 months of exercise training in healthy and obese individuals[7,19,30-33] while other studies did not show such an effect.[34-36] Such differences in effect may be due to either participant attributes, a technique of measurement to estimate HRV, study design, exercise types, and/or exercise dose parameter.[36]

A meta-analysis done using data from studies carried out in healthy people suggested that aerobic exercise training can make substantial improvements in the RR interval, and the effect size for changes in the RR interval recorded in this study was significantly higher in long exercise interventions (>12 weeks) than in shorter treatments (<12 weeks).[29] Meta-analysis including studies done in the elderly [37] suggested endurance-type exercise is effective for increasing HRV, and exercise frequency appears to be a powerful component of training that leads to HRV improvement.

A recent meta-analysis[19] reported improvement in HRV following weight-loss strategies such as dietary approaches, aerobic training, strength training, and exercise programs coupled with dietary approaches. Also, this study suggested that the impact of weight loss on the ANS might depend primarily on the amount of weight loss. Differences in the dosage of exercise, such as the duration, frequency, and strength of exercise training, are considered to be responsible for the degree of improvement in autonomic cardiac function and the change in body weight.[19]

The Exercise-based weight loss programs are known to be a key part of therapy for obesity and evaluating its impact on HRV would add value to current assessments of the evidence base. In addition, no studies to date have comprehensively analyzed and examined the evidence of exercise dose-response on HRV in people with overweight or obesity. Therefore, the objective of this review is to estimate the extent to which exercise-dose increases heart rate variability in individuals living with overweight and obesity class I and II.

METHODS:

Patient and Public Involvement:

No patient involved as it is a systematic review. The results will be disseminated by the publication of the manuscript in a peer-reviewed journal.

The Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) guidelines are used for the current study. PRISMA will be used to assist reporting of the SR, once completed.[38] This systematic review will consider only randomized controlled trials (RCTs). This systematic review is registered with PROSPERO (CRD42019104154). Any amendments to this study protocol will be reported.

Electronic Search:

Seven databases will be searched; PubMed/Medline, Scopus, EMBASE, ProQuest, CINAHL, Web of Science, and the Cochrane Library, for articles dating from 1965 to December 2021, since Hon and Lee[5] published their understanding of the clinical importance of heart rate variability in 1965. We will also refer to clinicaltrials.gov, the World Health Organization's registry platform ICTRP, the reference lists of key articles identified via Scopus, and articles that cited the included articles. Also, authors will be contacted to obtain for studies that have been completed but not published. If more than one publication describes the same study, the one that provides the most data will be included in the meta-analysis. Studies will be limited to publications in the English language. The search will be carried out by the first author and a medical librarian. Table 1 Shows the search strategy for PubMed.

Table 1 Shows the search strategy for PubMed

((((((((((((((((("exercise"[MeSH Terms]) OR exercise) OR exercise[Text Word]) OR exercise[Title]) OR exercise[Title/Abstract])) OR ((((aerobic exercise) OR aerobic exercise[Text Word]) OR aerobic exercise[Title]) OR aerobic exercise[Title/Abstract])) OR

((((resistance exercise) OR resistance exercise[Text Word]) OR resistance exercise[Title]) OR resistance exercise[Title/Abstract])) OR ((((concurrent exercise) OR concurrent exercise[Text Word]) OR concurrent exercise[Title]) OR concurrent exercise[Title/Abstract])) OR ((((combination exercise) OR combination exercise[Text Word]) OR combination exercise[Title]) OR combination exercise[Title/Abstract])) OR (((((“resistance training”[MeSH Terms]) OR resistance training) OR resistance training[Text Word]) OR resistance training[Title]) OR resistance training[Title/Abstract])) OR ((((aerobic training) OR aerobic training[Text Word]) OR aerobic training[Title]) OR aerobic training[Title/Abstract])) exercise dose OR dose response OR aerobic dose OR resistance dose OR concurrent dose OR combination dose OR (((((“cardiorespiratory fitness”[MeSH Terms]) OR cardiorespiratory fitness[Text Word]) OR cardiorespiratory fitness[Title]) OR cardiorespiratory fitness[Title/Abstract]) OR cardiorespiratory fitness)) OR ((((physical activity) OR physical activity[Text Word]) OR physical activity[Title]) OR physical activity[Title/Abstract])) OR ((((cardiorespiratory endurence) OR cardiorespiratory endurence[Text Word]) OR cardiorespiratory endurence[Title]) OR cardiorespiratory endurence[Title/Abstract])) OR ((((strength training) OR strength training[Text Word]) OR strength training[Title]) OR strength training[Title/Abstract])) OR ((((strengthening) OR strengthening[Text Word]) OR strengthening[Title]) OR strengthening[Title/Abstract])))

AND

(((((((“overweight”[MeSH Terms]) OR overweight) OR overweight[Text Word]) OR overweight[Title]) OR overweight[Title/Abstract])) OR (((((“obesity”[MeSH Terms]) OR obesity) OR obesity[Text Word]) OR obesity[Title]) OR obesity[Title/Abstract])) OR

((((healthy individuals[Text Word]) OR healthy individuals[Title]) OR healthy individuals[Title/Abstract]) OR healthy individuals)))

AND

(((((((((heart rate variability) OR heart rate variability[Text Word]) OR heart rate variability[Title]) OR heart rate variability[Title/Abstract])) OR ((((autonomic function) OR autonomic function[Text Word]) OR autonomic function[Title]) OR autonomic function[Title/Abstract])) OR ((((sympathetic function) OR sympathetic function[Text Word]) OR sympathetic function[Title]) OR sympathetic function[Title/Abstract])) OR ((((parasympathetic function) OR parasympathetic function[Text Word]) OR parasympathetic function[Title]) OR parasympathetic function[Title/Abstract])) OR ((((vagal function) OR vagal function[Text Word]) OR vagal function[Title]) OR vagal function[Title/Abstract]))

Eligibility Criteria and Study selection:

The titles and abstracts screening will be done for eligibility and the article considered appropriate will be reviewed in full-text papers. This process will be conducted using Covidence (www.covidence.org)[39] and it is expected to be completed by December 2021.

Inclusion Criteria:

Studies will be included if they report data from a) parallel-arm randomized trials (RCTs), b) enrolled adolescent (Age≥10 years) and adult individuals with overweight [BMI ≥ 25 – ≤29.9] and obesity [class I BMI: 30 - 34.9 and class II BMI: 35 - 39.9] undergoing aerobic or resistance exercise training or concurrent exercise training (Table 2)[40]

Table 2: Operational definitions of exercises type used for the current systematic review according to The American College of Sports Medicine. [40]

Exercise Type	Operational definition
Aerobic/endurance exercise training-	Aerobic exercise as any activity that uses large muscle groups, can be maintained continuously and is rhythmic in nature
Resistance/strength exercise training	Strength training that involves the performance of physical exercises which are designed to improve muscle strength and endurance
Concurrent exercise training	The combination of muscle strength and aerobic exercise during the same session or training program

and had an outcome of interest as HRV c) exercise intervention is reported in terms of frequency, intensity, time, and type, and d) measurement of at least one variable of HRV before and after the training intervention is reported.

Exclusion Criteria:

Exclusion criteria will be a) observational studies, b) studies measuring acute exercise effects, c) obesity class III (BMI ≥40) as it has been found that individuals living with severe obesity may have impaired autonomic function and this would confound the outcome of interest, and d) studies including individuals with cardiac, neurodegenerative, kidney or metabolic disease as they have an impact on autonomic function.[37,41-42]

Study Selection:

Following different database searches, retrieved articles will be imported to the Covidence platform[39] where the results will be combined and duplicates will be removed. As a large

number of papers are expected to require screening, four authors will be involved in screening. These authors will also perform pilot-testing of eligibility criteria on the first 10% of titles and abstracts. To harmonize the screening process, a training session will be provided to all reviewers. During this session reviewer will be asked to pilot-screen 15 titles/abstracts to prompt clarifications and screening decisions will be taken in compliance with inclusion/exclusion criteria. After scanning for titles and abstracts, articles that do not meet the inclusion requirements will be excluded and the remaining articles will have their full-text versions retrieved. The full-text screening will be done by two lead members of the synthesis team using the level of agreement between reviewers. Kappa statistics will be used to test the agreement [i.e. thresholds: <0.20 slight agreement, 0.21 - 0.40 fair agreement, 0.41 - 0.60 moderate agreement, 0.61 - 0.80 substantial agreement and >0.80 almost perfect agreement].[43] Disputes will be settled by agreement with the reviewers or by contacting an adjudicator. In a PRISMA flow chart, the study selection process is displayed.[44](Figure I)

Data extraction and analysis:

Outcomes:

In this study, the primary outcome of interest is the time domain (SDNN, SDANN, RMSSD, pNN50) and frequency domain variables of HRV (Total power, VLF, LF, HF, LF/HF ratio). (Table 3)

Table 3: Heart rate variability Domains.[5]

Secondary outcomes include Cardiorespiratory endurance, muscular strength, adiposity/anthropometric measures. These outcomes are chosen based on the previous research.[7,19,30-33] If data are available in qualifying studies, the relationship of exercise training with other endpoints, such as time effect and interaction effect with sociodemographic variables, anthropometric measures, presence of cardiovascular risk factors, diet, exercise adherence, and life stress, will also be analyzed.

Data extraction:

Time domain measures of HRV: Variable(units) and description	
SDNN (ms)	Standard deviation of all NN intervals
SDANN (ms)	Standard deviation of the averages of NN intervals
RMSSD (ms)	The square root of the mean of the sum of the squares of differences between adjacent NN intervals
pNN50 %	NN50 count divided by the total number of all NN intervals
Frequency domain measures of HRV: Variable(units) and description	
Total power ms^2	The variation of NN intervals over the temporal segment
VLF (ms^2)	Power in very low frequency range
LF (ms^2)	Power in low frequency range
HF (ms^2)	Power in high frequency range
LF/HF ratio	Ratio of LF and HF

A data extraction form will be adopted from published literature.[45-47] Data extraction process consists of manuscript title, author, time of publication, source of literature, characteristics of the trial (author, conducted/ publication year, duration, place of the trial conducted, number of participating centers, study design), the participants (sample size, participants randomized and patients analyzed in each group, age, sex, socioeconomic status, height, weight, body mass index, waist circumference, waist-hip ratio, waist-height

ratio, and body fat percent), intervention (aerobic, resistance, and concurrent exercise dose in terms of frequency, intensity, number of sessions, duration, and progression), control group treatment, method of randomization, method of allocation, blinding process, outcome time point and follow- up period, lack of follow-up or withdrawal, any incidental findings reported and the main outcome measurement heart rate variability reported either in absolute or log transformed or both. Two independent reviewers will pilot test the data extraction form and to resolve any disagreements team meetings will be conducted to refine the form. The two reviewers will perform data extraction separately. A training session will be held to harmonize the extraction of data, and at least two pilot extractions will be carried out to ensure accuracy. A written 'Data Extraction Guide' with detailed instructions will also be provided to reviewers. To assure accuracy, one lead member of the systematic review team will extract data from each article. An impartial third reviewer will cross-check the data extracted in duplicate. Inconsistencies in the data obtained will be resolved by agreement between the reviewers after reviewing the full-text article. When discrepancies occur, an adjudicator will be contacted. If the data published is incomplete or vague, the authors of the research will be contacted. Data extraction will be independently cross-checked.

Quality and Risk of bias assessment:

Two reviewers will independently review each selected article to eliminate bias. All selected articles will be evaluated for their quality based on the Cochrane Collaboration's Risk of Bias Tool 2.0 (RoB 2.0)[48] for risk of bias assessment across five domains. Assessments will be carried out using an iterative online form available.[49] The domain of missing outcome data will be evaluated, as per Akobeng and Ebrahim.[50-51] For each domain, the probability of

bias will be evaluated as 'low risk',' some concerns', or 'high risk'. If at least one area is listed as 'high risk,' studies will be deemed to have an overall high risk of bias. Quality of evidence will be measured using the GRADE rating system.[52] Publication bias will be evaluated using visual inspection of funnel plot asymmetry. [53]

Data synthesis Strategy: Meta-analysis:

We will primarily examine the training effect (aerobic, resistance, and concurrent exercise training) on HRV. We will also explore possible sources of heterogeneity among studies by examining aerobic, resistance, and concurrent exercise impact with time point. To attain the standardized mean difference and 95% confidence interval, the data of interest given as continuous will be used for meta-analysis. The Q-statistic and I^2 tests will be used to test for heterogeneity between the included studies. Heterogeneity will be considered low if I^2 is ≤ 40%, and high if I^2 is ≥ 75%. We will use a random-effects model for meta-analysis If substantial heterogeneity (I^2 >40 %) or fixed effects for homogeneous effects (I^2 <40%).[54] Aggregate data obtained from the included studies will be used for quantitative synthesis. By plotting the data on a forest plot, heterogeneity will be evaluated visually.[55]

Analysis of subgroups or subsets:

The sub-analysis will include baseline participant characteristics and exercise intervention characteristics. Interaction effects between variables will be identified for subgroup analysis.[55]

Significance:

Due to modernization and mechanization of lifestyle, there is an increase in overweight and obesity globally. Exercise is a key element to prevent lifestyle disease, therefore it is important to explore dose-response benefits specifically towards heart rate variability to maximize the physiological benefits. The study would help to understand the autonomic response of the heart (i.e., heart rate variability) at different doses of exercise training. Also can help to recommend the training regimen for overweight and obese people for optimum gain in heart rate variability

Ethics and dissemination:

This review will not require an ethical authorization, since participant privacy issues do not exist. Our results will provide data on the various forms of exercise dose-response on the HRV in overweight and obese people. The results of this study will be published in a peer-reviewed international journal, displayed at relevant conferences, and disseminated to obesity-focused public organizations.

Contributors:

SMK, KV, MA and MGA conceived of the study and provided guidance for drafting the protocol. MA and SMK designed the search strategy. SMK, KV, MA, KNS, SNR and MGA drafted and reviewed the final version systematic review protocol manuscript for submission. All the contributors read and approved the final manuscript.

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Patient consent for publication: not required

Availability of data and materials: For this study, data sharing is not applicable.

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Figure 1: Flow diagram for study selection based on the PRISMA guidelines: (Moher, Liberati, Tetzlaff, & Altman, 2009)

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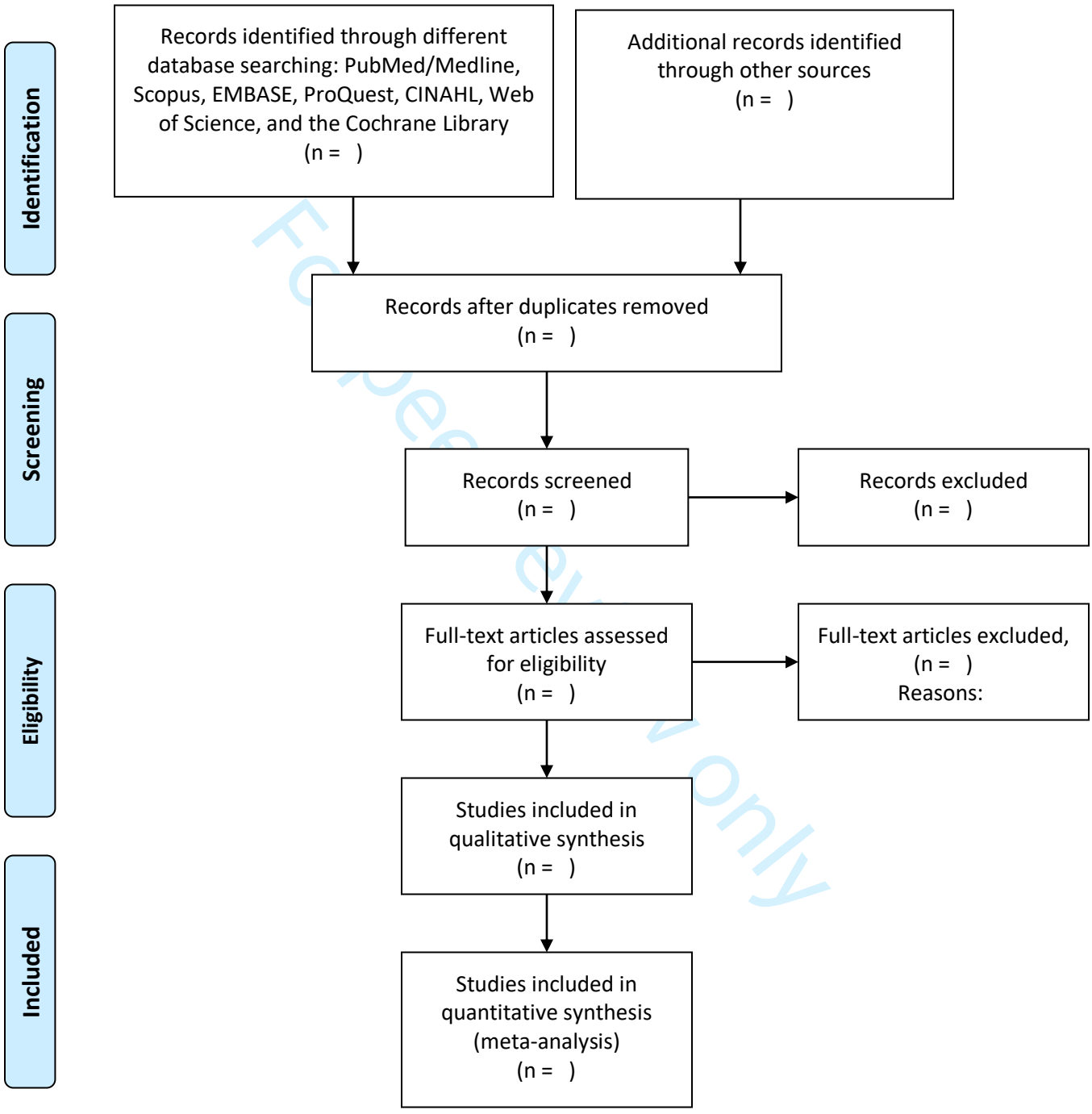

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

Reporting checklist for protocol of a systematic review.

Title: Exercise dose-response relationship with heart rate variability in individuals with overweight and obesity: Protocol for a systematic review and meta-analysis of randomized controlled trials

Based on the PRISMA-P guidelines.

		Reporting Item	Page Number
Identification	#1a	Identify the report as a protocol of a systematic review	1
Update	#1b	If the protocol is for an update of a previous systematic review, identify as such	NA
	#2	If registered, provide the name of the registry (such as PROSPERO) and registration number	2
Contact	#3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1& 2
Contribution	#3b	Describe contributions of protocol authors and identify the guarantor of the review	14
	#4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important	NA

		protocol amendments	
Sources	#5a	Indicate sources of financial or other support for the review	14
Sponsor	#5b	Provide name for the review funder and / or sponsor	NA
Role of sponsor or funder	#5c	Describe roles of funder(s), sponsor(s), and / or institution(s), if any, in developing the protocol	NA
Rationale	#6	Describe the rationale for the review in the context of what is already known	3-5
Objectives	#7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	5
Eligibility criteria	#8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	5-9
Information sources	#9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	5-9
Search strategy	#10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	5-7
Study records - data management	#11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	9-10
Study records - selection process	#11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	9
Study records - data collection process	#11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	10-12
Data items	#12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	10-11

Outcomes and prioritization	#13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	10-11
Risk of bias in individual studies	#14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	12
Data synthesis	#15a	Describe criteria under which study data will be quantitatively synthesized	12-13
	#15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I2, Kendall's τ)	12-13
	#15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	13
	#15d	If quantitative synthesis is not appropriate, describe the type of summary planned	12-13
Meta-bias(es)	#16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	12
Confidence in cumulative evidence	#17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	12